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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,002	05/30/2001	Brett P. Monia	ISPH-0578	9404

26259 7590 04/16/2003

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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT PAPER NUMBER

1634

DATE MAILED: 04/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/870,002

Applicant(s)

MONIA ET AL.

Examiner

Jeffrey Fredman

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21 and 22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21 and 22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Status

1. Claims 21 and 22 are pending.

Claims 1-20 are cancelled.

Claims 21 and 22 are rejected.

Priority

2. Applicant cancellation of the priority claim is acknowledged.

Claim Rejections - 35 USC § 102

3. The rejection of claims 12-20 under 35 U.S.C. 102(b) is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al (WO 94/08625) in view of Possinger et al (Anti-cancer Drugs (1995) 6:suppl 6 pp. 55-59).

Calabretta teaches a method for inhibiting the proliferation of cancer cells comprising modulating the expression of human ras, including N-ras, H-ras and K-ras (see page 16, lines 1-9, page 85-86, claims 16 and 17) comprising:

(a) contacting tissue or cells containing a human ras gene (see page 13, lines 19-37 and page 16, lines 1-9) with an effective amount of a composition comprising an oligonucleotide which is targeted to a nucleic acid encoding human ras and which is capable of inhibiting ras expression (see page 13, lines 19-37, page 16, lines 1-9 and page 17, line 4 to page 22, line 2, page 85-86, claims 16 and 17) and at least one chemotherapeutic agent (see page 22, line 14 to page 23, line 25, page 85-86, claims 16 and 17),

whereby expression of ras is modulated and proliferation of cancer cells is inhibited (see page 16, lines 1-9, page 85-86, claims 16 and 17).

Calabretta teaches the use of an amount which kills cancer cells while sparing normal hematopoietic (blood) cells (see page 14, lines 8-17).

Calabretta expressly teaches that the method can be used to treat diseases (see page 31, lines 10-24) including ras associated diseases such as the hyperproliferative condition of colon cancer (see page 32, lines 14-17).

Calabretta teaches purging of bone marrow (see page 38, lines 12-31) which inherently comprises some peripheral blood mononuclear cells.

While Calabretta expressly suggests combination therapy using the antisense oligonucleotides with chemotherapeutic agents including antimetabolites (See page 22, lines 1-22), Calabretta does not teach combination of the antisense with the antimetabolite Gemcitabine for cancer treatment.

Possinger teaches the use of Gemcitabine for treatment of cancer (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Calabretta to use Gemcitabine in the combination therapy since Calabretta expressly teaches "The non-antisense component of the therapeutic combination may comprise an antineoplastic (anti cancer) agent useful in the treatment of the particular disease state characterized by the expression of the targeted oncogene/proto-oncogene (see page 22, lines 5-9)". Calabretta further notes that H-ras is associated with breast cancer (see page 32, line 16). Motivation to use Gemcitabine in combination with the antisense is derived from Possinger who states "Gemcitabine's modest toxicity profile and single-agent activity make it an attractive candidate for trial in combination therapy in advanced breast cancer (abstract)". Possinger also notes that "Gemcitabine is a logical candidate for combination chemotherapy (see page 59, column 1)". An ordinary practitioner would

have been motivated to use the antimetabolite Gemcitabine in the place of other antimetabolites expressly recited by Calabretta in his combination therapy for treatment of H-ras based cancers since Gemcitabine is expressly suggested by Possinger for use in combination therapies such as those of Calabretta and since Gemcitabine has low toxicity and good activity against cancer.

Response to Arguments

4. Applicant's arguments filed on March 20, 2003 have been fully considered by the examiner but are not persuasive for the following reasons.

Applicant argues that there is no motivation to combine the method of Calabretta and the teaching of Possinger to combine treatment of cancer with antisense to Ras and the antimetabolite drug, Gemcitabine since no data is provided in the references showing in vivo activity. Thus, Applicant is arguing that there is no motivation to combine and no reasonable expectation of success.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it is noted that there is express motivation to combined provided in the rejection. Specifically, the rejection notes that Calabretta teaches and suggests the use of combination therapy for

cancer using a Ras antisense oligonucleotide and an antimetabolite compound. One such antimetabolite is Gemcitabine, which Possinger expressly teaches and suggests is suitable for combination therapy for cancer with other agents. Thus, an ordinary practitioner would have been motivated to use the antimetabolite Gemcitabine in the place of other antimetabolites expressly recited by Calabretta in his combination therapy for treatment of H-ras based cancers since Gemcitabine is expressly suggested by Possinger for use in combination therapies such as those of Calabretta and since Gemcitabine has low toxicity and good activity against cancer.

With regard to Applicant's argument that there was no reasonable expectation of success, this requirement is derived from the caselaw. The Federal Circuit in In re O'Farrell, 853 F.2d 894, 903, 904 (Fed. Cir. 1988) noted

"The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. (citations omitted). In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (citations omitted). Neither of these situations applies here."

Following the analysis of In re O'Farrell, in this instance the prior art references of Calabretta and Possinger do not suggest varying a variety of parameters in which the prior art gave no indication of critical parameters. Here, Calabretta specifically disclosed that combination treatments were desirable to treat cancer noting that "The

combination of agents is more efficient in the elimination of neoplastic cells at concentrations which are substantially less toxic to normal hematopoietic cells populating the marrow (page 14, lines 5-8).” Thus Calabretta expressly shows the expectation of success in combination of an antisense agent and a chemotherapeutic agent. The prior art of Calabretta expressly suggested the use of Ras antisense and antimetabolites for treatment, while the prior art of Possinger expressly directed the practitioner to combination therapy with Gemcitabine. Possinger notes that “Gemcitabine is a logical candidate for combination chemotherapy (see page 59, column 1)”. With regard to the the issue of general guidance, both Calabretta and Possinger give specific guidance as already noted to combine the antisense agent with the logical candidate, Gemcitabine. Thus, as in O’Farrell, neither of the “obvious to try” situations occurs here, since there is specific and direct teaching of the parameters of the invention with specific guidance to select the Ras antisense and Gemcitabine in combination.

Conclusion


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jeffrey Fredman
Primary Examiner
Art Unit 1637

April 15, 2003